EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 8 Cases*	

GENERAL EXPERT REPORT OF AHMET BEDESTANI, M.D.

I make this report and hold all opinions stated herein to a reasonable degree of medical certainty. A copy of my curriculum vitae is attached hereto as Exhibit A. The materials I reviewed and relied on in reaching the opinions set forth in this report are listed in Exhibit B. Exhibit C to this report is a slide deck I compiled in conjunction to the preparation of this report. These slides contain additional materials I've reviewed, referenced and relied upon in the preparation of this report. The compensation for my review and input in this legal matter will be billed at a rate of $500 per hour. My rate for providing testimony by deposition is $1000 per hour.

I attended Saint Louis University for my undergraduate degree in biology and then attended Saint Louis University School of Medicine for a Certificate in Human Anatomy before returning to Saint Louis University Graduate School for a Master's degree in Molecular Biology. I attended Ross University School of Medicine followed by residency in Obstetrics and Gynecology at the Mount Sinai School of Medicine Queens Hospital program in Queens, New York. I completed a fellowship in Female Pelvic Medicine and Reconstructive Surgery at Louisiana State University School of Medicine, Department of Obstetrics and Gynecology, in New Orleans, Louisiana. I attained dual board status through the American Board of Obstetrics and Gynecology in Obstetrics and Gynecology, as well as in Female Pelvic Medicine and Reconstructive Surgery and Gynecology. I have more than 15 years' experience in the diagnosis and treatment of female urinary incontinence and pelvic disorders. This experience includes taking histories, performing physical exams, and ordering and conducting diagnostic testing, including urodynamic testing. I am familiar with the potential risks and complications associated with both nonsurgical and surgical treatment of incontinence disorders. I am actively performing prolapse and incontinence surgery as well as many other procedures related to diseases of the female pelvis.

I have performed various types of surgery for the correction of stress urinary incontinence and pelvic organ prolapse, including native tissue repair, autologous fascial slings, open and laparoscopic Burch urethropexies, and synthetic mesh slings in addition to mesh augmented repair of pelvic organ prolapse. I am quite comfortable with the midurethral slings made from polypropylene, as well as polypropylene used in the repair of pelvic floor defects. I have experience and a thorough understanding of the mechanism and safety profile of Prolene mesh material as it applies to midurethral slings and pelvic prolapse. I have performed over 1000 midurethral slings and over 1000 surgeries to correct pelvic organ prolapse. Over the last 6 years, my practice has added robotic-assisted approaches to the surgical management of pelvic organ prolapse.

Overview of Opinions

Female pelvic organ prolapse can be found described as early as 400 BC by Hippocrates. The paper by Dr. George Orwell describing a radical cure of cystocele by suturing the lateral sulci of the Vagina to white line of pelvic area. appears in scientific literature in 1909. Despite all of humanity's advancements in technology, science, and medicine prolapse of the pelvic organs still remains a common occurrence with high levels of recurrence after surgical management. Such a high frequency of incidence leads to a global health issue with significant morbidity.

Historically surgical management of female pelvic working prolapse has relied on native tissue repairs, with some techniques dating back over 100 years. As a result of such surgeries having high unacceptable failure rates with associated morbidity, surgeons looked to incorporating different types of grafts to augment their repairs in hopes of improving the longevity of their repairs, while at the same time decreasing complications.

Taking inspiration from the field of abdominal hernia repair pelvic surgeons adopted grafts into their armamentarium and modified materials and techniques to meet their needs. Through meticulous study, research and refinement the field of material science brought fourth different types of grafts. As data was gained on such materials their utilization profiles were refined and their affects on patients noted. Such data was utilized to refine the different types of meshes of which at one time over 70 different ones were available. Through the crucible of time and observation some were found to have a negative impact on their human hosts while others were found to be safe and efficacious.

Before Prosima was ever even imagined physicians were utilizing mesh to augment their anterior and posterior repairs. Through the advancement of science it was found that macroporous monofilament with specific characteristics were desirable for pelvic organ prolapse repair. With the best of intentions GYNEMESH PS was developed to meet a need. Its fibers are identical in composition to PROLENE suture material.

Grafts were incorporated into native tissue repair techniques and after initial positive outcome, kits were developed of which there were several. All except Prosima mimicked certain aspects of specific native tissue repairs in violating the sacrospinous ligament complex.

PROSIMA:

- Tested and found to be safe in early observational studies as well as larger scale studies
- Appropriately manufactured
- Appropriately sterilized
- Appropriately packaged
- Is not defectively designed
- A leap ahead utilizing the vaginal support device to extrinsically complete the repair through positive pressure vector molding of the tissue repair cycle.
- Safe from an anatomical perspective. Unlike sacrospinous ligament fixation or all the other trocar based mesh delivery systems PROSIMA did not violate the sacrospinous ligament and as such avoided significant neurovascular structures, Additionally, PROSIMA did not violate the obturator fascia, nor muscle.
- Instructions for use were appropriate
- Ethicon supported physician appropriately with proper training.
- At the time of release it represented an appropriate approach to the management of Stage 2 and Stage 3 prolapse

Based on my education, training, experience and extensive review of the medical literature, I believe to a reasonable degree of medical and scientific certainty that the PROSIMA system represented a safe, appropriate option for women who suffered from moderate pelvic organ prolapse.

By way of background, I've included the below paper I wrote that was published in the East Jefferson General Hospital Medical Journal. The paper serves as a helpful overview of pelvic organ prolapse.

Pelvic Organ Prolapse: Demographics, Symptomatology,and Anatomical Considerations

Ahmet Bedestani, M.D., Urogynecology

Within the female pelvis three tiers of support comprised of bone, muscle, and connective tissue work in concert to support the pelvic organs (uterus, vagina, bladder, bowel, rectum, and anus) in a specific three-dimensional orientation to facilitate locomotion, copulation, parturition while maintaining continence of flatus, urine, and feces. Pelvic organ prolapse (POP)occurs when one or more of the pelvic organs move out of normal anatomical orientation allowing for delineation into apical, anterior, and posterior prolapse.

Apical prolapse occurs when the uterus, or vaginal cuff, in cases of previous hysterectomy, migrates out of position; anterior vaginal defects result when the bladder or urethra are displaced resulting in a cystocele, or urethrocele, respectively. Posterior vaginal defects can be created by protrusion of rectum into the vaginal lumen resulting in a rectocele. Small bowel displacement can occur through any of the three compartments resulting in an apical, anterior, or posterior enterocele.

Such defects can exist in isolation or in combination resulting in a clinical continuum of symptomology affecting millions of American women that increases with age and adversely affects quality of life and sexual function. If conservative treatments fail, then surgical management must be considered to address specific defects of support to satisfy realistic patient expectations of symptom relief.

Pelvic organ prolapse is common and is seen on examination in 40% to 60% of parous women, with further refinement of prevalence achieved through the analysis of specific clinical populations requesting gynecologic services, and databases on surgeries with pelvic organ prolapse (POP) as a clinical indication.[1] (1). Loss of vaginal or uterine support in women presenting for routine gynecological care is seen in up to 43-76% of patients, with 3-6% having descent beyond the hymen.[2] (2). In the Women's Health Initiative, 41% of women age 50-79 years showed some amount of pelvic organ prolapse, including cystocele in 34%, rectocele in 19%, and uterine prolapse in 14%.[3] (3). In a multicenter study of 1006 women age 18- 83 years presenting for routine gynecological care, 24% had normal support and 38% had stage I, 35% stage II, and 2% stage Ill pelvic organ prolapse.[4] (4).

In order to appreciate the spectrum of POP one must be able to measure the amount of anatomic abnormality. The Pelvic Organ Prolapse Quantification system (POP-Q) (Figure 1) refers to an objective, site-specific system for describing, quantifying, and staging pelvic support in women.[5] (5). It provides a standardized tool for documenting, comparing, and communicating clinical findings with proven interobserver and intraobserver reliability, which has led to its adoption by the International Continence Society (ICS), the American Urogynecologic Society (AUGS), and the Society of Gynecologic Surgeons for the description of female pelvic organ prolapse.[6] (6). Other prolapse staging systems predate the quantification system and are shown in comparison to the POP-Q stages (Figure 2). While the evolution of

[1] Handa VL, Garrett E, Hendrix S, Gold E, Robbins J. Progression and remission of pelvic organ prolapse: a longitudinal study of menopausal women. Am J Obstet Gynecol 2004;190 (1):27- 32

[2] Swift S, Woodman P, O'Boyle A, et al. Pelvic Organ Support Study (POST): the distribution, clinical definition, and epidemiologic condition of pelvic organ support defects. Am J Obstet Gynecol 2005; 192: 795-806

[3] Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002; 186: 1160-6

[4] Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol 2003; 189: 372-7

[5] Bump RC, Mattiasson A, Bo K, Brubaker LP, Delancey JO, Klarskov P, Shull BL. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175(1):10-17

[6] Hall AF, Theofrastous JP, Cundiff GW, Harris RL, Hamilton LF, Swift SE, Bump RC. lnterobserver and intraobserver reliability of the proposed Interna tional Continence Society, Society of Gynecologic Surgeons, and American Urogynecologic Society pelvic organ prolapse classification system. Am J Obstet Gyneco/ 1996;175(6):1467 -70

grading systems for POP has spanned the last 50 years, its measured pathology has been in existence for a much longer period of time.

History

In 400BC, Hippocrates described prolapse, but the pathogenesis was not understood, and effective treatment was elusive with not much change over the next 1800 hundred years. Even today the lifetime risk that a woman in the United States will have surgery for prolapse or urinary incontinence is 11%, with up to one third of surgeries representing repeat procedures.[7] (7). Data from the U.S. National Hospital Discharge Survey reported that approximately 200,000 women undergo surgery for POP annually.[8] (8).

Prevalence

This number will continue to grow as women live longer and expect a higher quality of life free of the symptoms of POP (Table 1) as they peruse an active lifestyle with the expectation of sexual activities. This is based on projections from the United States Census Bureau, where the number of American women aged 65 years and over will double in the next 25 years, to more than 40 million women by 2030.[9] (9). By one estimate, the demand for health care services related to pelvic floor disorders will increase at twice the rate of the population itself.[10] (10). This will lead to an acceleration of healthcare expenditure, which in 1997 stood at a billion dollars for 225,000 inpatient surgical procedures for POP in the USA (22·7 per 10,000 women).[11] (11).

[7] Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997;89:501-6

[8] Boyles SH, Weber AM, Meyn L. Procedures for pelvic organ prolapse in the United States, 1979- 1997. Am J Obstet Gynecol 2003;188:108 -15

[9] U.S. Census Bureau. U.S. Interim projections by age, sex, race, and Hispanic origin. Available at: http://www.census.gov/ipc/www/usinterimproj. Retrieved June 28, 2005

[10] Luber KM, Boero S, Choe JV. The demographics of pelvic floor disorders: current observations and future projections. Am J Obstet Gynecol 2001;184:1496-1503

[11] Subak LL, Waetjen LE, van den Eeden S, Thom DH, Vittinghoff E, Brown JS. Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol 2001; 98: 646-51

Despite its history, prevalence, and consumption of health care resources, the definitive causes of POP are not known, but are thought to be multifactorial with advancing age, vaginal childbirth, and obesity being the most established risk factors. The Women's Health Initiative noted that single childbirth was associated with an increased risk of uterine prolapse, and every additional delivery up to five births increasing the risk of prolapse by 10-20%.[12] (12). This does not mean that nulliparity is protective against prolapse as almost one fifth of nulliparous women in the same study had some degree of prolapse.[13] (13). The contribution of weight to POP is more direct as the same study was significant for women with a body mass index greater than 30 kg/m2 having a 40-75% increased risk of prolapse.[14] **(14).**

Other risk factors for the development of prolapse can be classified as predisposing (genetic, race, and gender); inciting (pregnancy & childbirth, surgery such as hysterectomy for prolapse, myopathy, and neuropathy); promoting (obesity, smoking, pulmonary disease, constipation, chronic straining, recreational or occupational activities), or decompensating (aging, menopause, debilitation, medication) events.[15] (15).

Table 1. Potential Risk Factors for Pelvic Organ Prolapse

Predispose	Incite	Promote	Decompensate
Genetic (congenital or hereditary)	Pregnancy and delivery	Obesity	Aging
Race: White > African-American	Surgery such as hysterectomy for prolapse		
Smoking	Menopause		
Gender: Female > Male	Myopathy	Pulmonary disease (chronic coughing)	
	Neuropathy		
	Neuropathy	Constipation (chronic straining)	Myopathy
		Recreational or occupational activities (frequent or heavy lifting)	
Debilitation			
Medication			

Adapted from Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:723–46. Copyright 1998, with permission from Elsevier.

[12] Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002; 186:1160-6

[13] Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002; 186:1160-6

[14] Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. Am J Obstet Gynecol 2002; 186:1160-6

[15] Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:723-46

While epidemiology has provided insight into the prevalence and possible risk factors for POP, the exact delineation between normal variation of pelvic support and a pathological state is not clearly defined, as only weak-to-moderate correlations exist between severity or stage of prolapse and presence of specific symptoms such as bulging, heaviness, and voiding dysfunction.[16] (16). Although many of these symptoms are correlated to some extent with presence and severity of prolapse, the only one that is acknowledged consistently by patients with severe prolapse is presence of a vaginal bulge that can be seen or felt.[17] (17).

Such unclear association between documented anatomic abnormality and symptomology is evident in the relationship of pelvic and low back pain with POP. A recent study found pelvic pain was not associated with prolapse, and women with more advanced prolapse actually had less back pain than women with mild prolapse.[18] (18). The hymen, however, seems to be an important boundary point for the development of POP disorders, as the average number of positive responses in a patient-directed questionnaire per subject for POP symptoms was 0.27 for stage 0, 0.55 for stage I, 0.77 for stage II, and

2.1 for stage Ill where the leading edge of the prolapse extended beyond the hymen.[19] (19).

Typical Symptomology

Symptoms listed in Table 1 could be attributable to the anatomic displacement of the vagina, or to dysfunction of the affected organ systems such as the lower urinary tract, colon, rectum, or the muscles of the pelvic floor. Patient perceptions, however, are not specific to different compartments of prolapse but may reflect the overall stage of POP at its most advanced site.[20] (20). Anatomical derangement of any compartment can occur in isolation, as

[16] Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001; 185: 1332-7
[17] Samuelsson EC, Arne Victor FT, Tibblin G, Svardsudd KF. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am J Obstet Gynecol 1999; 180: 299-305
[18] Heit M, Culligan P, Rosenquist C, Shott S. Is pelvic organ prolapse a cause of pelvic or low back pain? Obstet Gynecol 2002;99:23-8
[19] Swift SE, Tate SB, Nicholas J. Correlation of symptoms with degree of pelvic organ support in a general population of women: what is pelvic organ prolapse? Am J Obstet Gynecol 2003; 189:372-7
[20] Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001; 185: 1332-7

shown by the cystocele, enterocele, and rectocele in picture 1, or in combination leading to complex prolapse with an increased range of symptoms experienced by the patient. Examples of this can be seen patients with apical and anterior prolapse, who present with urinary symptoms ranging from stress urinary incontinence to difficulty initiating micturition.

Anatomical Findings

Coexistence of urinary incontinence and POP can possibly be explained by loss of anterior compartment support leading to urethral hypermobility and cystocele formation, which is thought to contribute to development of stress urinary incontinence.[21] (21). This is an oversimplification as some women have stress incontinence symptoms due to urethral incompetence, but as POP extends beyond the hymen patients are less likely to experience stress incontinence and more likely to have symptoms of obstructed voiding, such as urinary hesitancy, intermittent flow, weak or prolonged stream, a feeling of incomplete emptying, need to manually reduce (splint) the prolapse to initiate or complete urination and, in rare cases, urinary retention.[22,23] (22, 23). In one study, urethral obstruction occurred in 58% of women with grade 3 and 4 anterior vaginal prolapse, compared with 4% in women with grade 1 and 2 prolapse, with 30% of women with stage Ill or IV prolapse having raised post-void residual volumes (>100 ml). [24,25] (24,25). The mechanism for urinary retention seems to be mechanical obstruction resulting from urethral kinking that arises with progressively worsening anterior vaginal prolapse, leading to women with advanced anterior compartment defects being continent.

In some women, this reflects normal urethral sphincter competence despite lack of support. In other cases, women with urethral incompetence are continent only because the prolapse causes urethra l kinking and

[21] Delancey JO. Structural support of the urethra as it re lates to stress urinary incontinence: the hammock hypot hesis. Am J Obstet Gynecol 1994; 170: 1713-20
[22] Burrows U, Meyn LA, Walters MD, Weber AM. Pelvic symptoms in women with pelvic organ prolapse. Obstet Gynecol 2004; 104: 982-8
[23] Barber M, Walters MB, Bump R. Association of the magnitude of pelvic organ prolapse and presence and severity of symptoms. J Pelvic Med Surg 2003; 9: 208
[24] Romanzi U, Chaikin DC, Blaivas JG. The effect of genital prolapse on voiding. J Urol 1999;161:581-6
[25] Coates KW, Harris RL, Cundiff GW, Bump RC. Uroflowmetry in women with urinary incontinence and pelvic organ prolapse. Br J Urol 1997; 80: 217-21

obstruction.[26] (26). This is called potential, masked, latent, or occult stress incontinence because women do not have symptoms of incontinence as long as the prolapse is untreated.

In complex POP cases urinary symptoms should not be attributed solely to anterior and apical defects, as large posterior vaginal prolapse can also cause mechanical obstruction by direct urethral compression.[27] (27). Similarly, defecatory symptoms related to bowel dysfunction, (including a feeling of incomplete emptying, straining, need to apply digital pressure to the vagina or perineum (splint) to start or complete defecation, urgency, and fecal incontinence) should not be automatically attributed to defects of the posterior compartment. In studies of the relationship between bowel dysfunction and presence and severity of prolapse, researchers have reported either a weak correlation between posterior vaginal wall support and specific anorectal symptoms or no link at all, with the need to splint being the most consistently associated with posterior POP.[28,29,30] (28-30). This is not a constant relationship as most women with rectoceles do not have this symptom, and some without a posterior defect also use manual pressure to accomplish defecation.[31,32] (31,32).

Additionally, 7-31% of women with pelvic organ prolapse report fecal incontinence.[33] (33). Such an association should not automatically be attributed to defects of the posterior vaginal compartment. While rectal prolapse is a recognized cause of fecal incontinence, the role vaginal support

[26] Bump RC, Fanti JA, Hurt WG. The mechanism of urinary continence in women with severe uterovaginal prolapse: results of barrier studies. Obstet Gynecol 1988;72:291-5
[27] Barber MD. Symptoms and outcome measures of pelvic organ prolapse. Clin Obstet Gynecol 2005; 48: 648-61
[28] Ellerkmann RM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001; 185: 1332-7
[29] Burrows U, Meyn LA, Walters MD, Weber AM. Pelvic symptoms in women with pelvic organ prolapse. Obstet Gynecol 2004; 104: 982-8
[30] Barber M, Walters MB, Bump R. Association of the magnitude of pelvic organ prolapse and presence and severity of symptoms. J Pelvic Med Surg 2003; 9: 208
[31] Spence-Jones C, Kamm MA, Henry MM, Hudson CN. Bowel dysfunction: a pathogenic factor in uterovaginal prolapse and urinary stress incont inence. Br J Obstet Gynaecol 199 4; 101: 147-5
[32] Weber AM, Walters MD, Ballard LA, Booher DL, Piedmonte MR. Posterior vaginal prolapse and bowel function. Am J Obstet Gynecol 1998; 179: 1446-9
[33] Jackson SL, Weber AM, Hull TL, Mitchinson AR, Walters MD. Fecal incontinence in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol 1997; 89: 423-7

defects play in this pathology has not been fully established. Continence of stool depends on normal mental function, volume and stool consistency, colonic transit time, anorectal sensation and reflexes, rectal distensibility, and anal sphincter function. Degradation of any of those factors can contribute to development of fecal incontinence. The coexistence of POP and fecal incontinence is not a simple cause and effect relationship but rather coexistence as a result of common risk factors such as neuropathic and muscular injury to the pelvic floor along with the effects of aging.[34] (34).

With such an array of symptoms and possibility of urinary or fecal incontinence the influence of prolapse on sexual functioning should be addressed in women of all ages, as some women with prolapse avoid vaginal intercourse out of concern or embarrassment.[35] (35). A third of sexually active women with pelvic organ prolapse complain that their prolapse interferes with sexual function.[36] (36). This does not mean there is a linear relationship between coital difficulty and POP, as a high rate of sexual satisfaction (81- 84%) has been reported in women with pelvic organ prolapse who are in an intimate relationship.[37] (37).

Assessing sexual function is particularly important before and after surgery, so that any potentially adverse effects can be recognized and addressed.[38] (38). The preservation of coital capacity, if it is the patient's wish to do so, must be taken into account in the management of all aspects of POP to prevent de novo dyspareunia or a worsening of it. Conversely, the restoration of normal anatomy is not a cure for painful intercourse, nor will it improve sexual function leading to greater satisfaction. In a comparison of sexual function in individuals with and without prolapse, using a validated sexual-function questionnaire, no difference was noted in frequency of intercourse, libido,

[34] Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1998;25:723-46

[35] Handa Vl, Harvey L, Cundiff GW, Siddique SA, Kjerulff KH. Sexual function among women with urinary incontinence and pelvic organ prolapse. Am J Obstet Gynecol 2004;191:751-6

[36] Weber AM, Walters MD, Piedmonte M R. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2000; 182:1610-5

[37] Barber MD, Visco AG, Wyman JF, Fanti JA, Bump RC. Sexual function in women with urinary incontinence and pelvic organ prolapse. Obstet Gynecol 2002; 99: 281-9

[38] Weber AM, Walters MD, Piedmonte M R. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2000; 182:1610-5

vaginal dryness, dyspareunia, orgasmic function, or overall sexual function between the two groups.[39] (39).

A pelvic surgeon must be able to elicit a comprehensive medical history that identifies all pelvic floor disorders, and perform a pelvic examination including assessment of uterovaginal support, pelvic muscle strength, neurological status, uterine and ovarian size. Additionally, the vaginal apex, anterior wall, bladder neck, posterior wall, perineum, and possible presence of an enterocele must all be taken into account. Symptoms combined with physical findings, along with an understanding of the interplay between abnormal anatomic support and physiologic function of the pelvic musculature, vagina, bladder, and rectum will lead to the establishment of realistic treatment plans to meet the needs of patients. If surgical intervention is called for then perioperative discussion points to have with the patient must include presence of sexual activity, need for concomitant total or subtotal hysterectomy, route of surgery (Transvaginal, Laparotomy, Laparoscopic, or Robotically Assisted), native tissue repair versus graft augmentation of the reconstruction, presence of occult urinary incontinence, long-term outcomes, and the de novo development of functional derangements as a result of the repair. Such information is needed to establish realistic outcome expectations in the pursuit to reestablish normal anatomy, maintain or restore standard bowel and bladder function, and maintain vaginal capacity for sexual intercourse, if desired.

As baseline health in the elderly population continues to improve, the number of women in the United States with symptomatic pelvic organ prolapse ("POP") will increase by approximately 50% by 2050[40].

Some of the typical symptoms associated with POP are identified in the table below:

[39] Weber AM, Walters MD, Schover LR, Mitchinson A. Sexual function in women with uterovaginal prolapse and urinary incontinence. Obstet Gynecol 1995; 85: 483-7

[40] ACOG Committee on Practice Bulletins-Gynecology, American Urogynecologic Society. ACOG Practice Bulletin No. 185: Pelvic organ prolapse. Obstet Gynecol. 2017;130(5):e234-e250

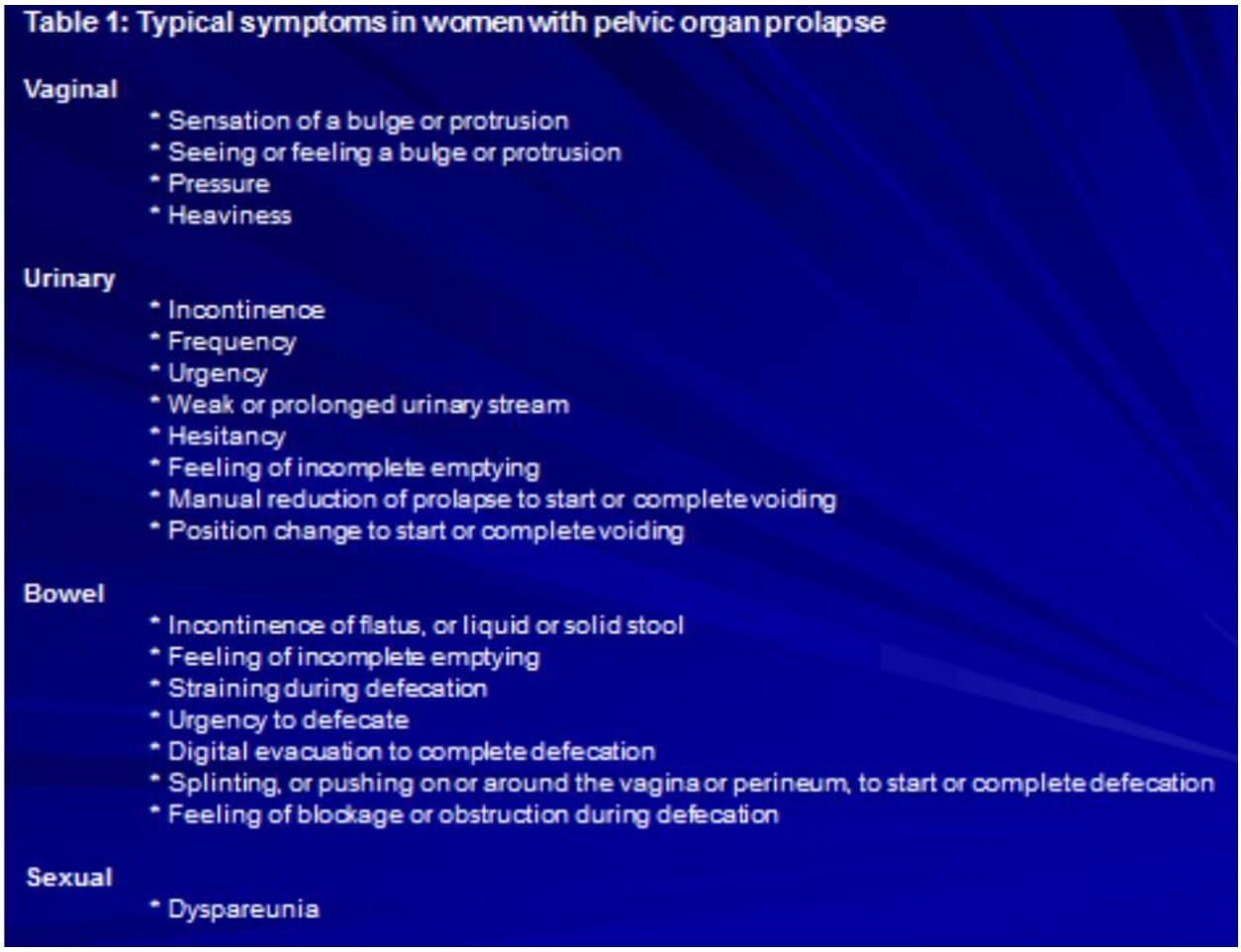

Table 1: Typical symptoms in women with pelvic organ prolapse

Vaginal

- Sensation of a bulge or protrusion
- Seeing or feeling a bulge or protrusion
- Pressure
- Heaviness

Urinary

- Incontinence
- Frequency
- Urgency
- Weak or prolonged urinary stream
- Hesitancy
- Feeling of incomplete emptying
- Manual reduction of prolapse to start or complete voiding
- Position change to start or complete voiding

Bowel

- Incontinence of flatus, or liquid or solid stool
- Feeling of incomplete emptying
- Straining during defecation
- Urgency to defecate
- Digital evacuation to complete defecation
- Splinting, or pushing on or around the vagina or perineum, to start or complete defecation
- Feeling of blockage or obstruction during defecation

Sexual

- Dyspareunia

Non-surgical treatment options for pelvic organ prolapse

A pelvic surgeon must be able to elicit a comprehensive medical history that identifies all pelvic floor disorders, and perform a pelvic examination including assessment of uterovaginal support, pelvic muscle strength, neurological status, uterine and ovarian size. Additionally, the vaginal apex, anterior wall, bladder neck, posterior wall, perineum, and possible presence of an enterocele must all be taken into account. Symptoms combined with physical findings, along with an understanding of the interplay between abnormal anatomic support and physiologic function of the pelvic musculature, vagina, bladder, and rectum will lead to the establishment of realistic treatment plans to meet the needs of patients.

Management of pelvic organ prolapse can be divided into three broad categories consisting of observation, conservative therapies and active surgical management. Observation can be utilized for patients whose anatomic defects are not bothersome enough to require active surgical management. There is almost no indication for asymptomatic prolapse treatment. Conservative therapy can also be referred to as nonsurgical management which involves the utilization of pessaries, pelvic floor physical therapy and adjunct therapy to address urinary, defecatory and sexual dysfunction. The goal of such management being to reduce the severity of symptoms to delay or even avoid surgical intervention.

If surgical intervention is called for then perioperative discussion points to have with the patient must include presence of sexual activity, need for concomitant total or subtotal hysterectomy, route of surgery (Transvaginal, Laparotomy, Laparoscopic, or Robotically Assisted), native tissue repair versus graft augmentation of the reconstruction, presence of occult urinary incontinence, long-term outcomes, and the de novo development of functional derangements as a result of the repair. Such information is needed to establish realistic outcome expectations in the pursuit to reestablish normal anatomy, maintain or restore standard bowel and bladder function, and maintain vaginal capacity for sexual intercourse, if desired.

Surgical treatment options

Over the years, numerous techniques—some vaginal, some abdominal—were developed to treat POP. Some of these surgeries involve incisional approaches, others are performed laparoscopically. Basic rectocele and cystocele repairs traditionally were treated through a simple colporrhaphy procedure. These procedures, though, carried with them a 30-50% failure rate as demonstrated in multiple different studies. Other surgical options have included the uterosacaral ligament repairs and the sacrospinous ligament fixation procedures. These surgeries have demonstrated improved success rates over colporrhaphies but carry with them potential risks of significant injury to internal structures and nerves, resulting in pain, dyspareunia, infection, urinary problems, and damage to adjacent organs. The abdominal sacrocolpopexy has a higher success rate but also carries with the significant potential complications. When performed in the open fashion it induces significant morbidity given the level of dissection required. When performed laparscopically, the morbidity is reduced but the potential complications still exist and the economic cost is exceedingly high.

Given the historically high rate of failure associated with these procedures—especially colporrhaphies and suture fixation procedures—surgeons looked to biologic and synthetic graft materials to reinforce their repairs and hopefully improve the durability and efficacy of their procedures. While mesh procedures naturally introduced the new potential risk of mesh erosion or extrusion, they otherwise presented the same potential risks and complications that had been associated with all other non-mesh surgeries to treat POP. Mesh erosion in POP surgeries has proven to range from as low as 0% to higher than 30%. This, in my opinion, largely reflects the importance of surgeon skill and technique—the better the technique, the lower the mesh erosion rate will be. When erosion occurs, it is often easily managed with estrogen cream, and is often asymptomatic. That said, there is no way to surgically treat POP without incurring the risk of pain (even chronic pain), dyspareunia, infection, urinary problems, scarring, and recurrence. To claim that the fact that any of these complications occur means that a mesh product is defective is to call for all pelvic floor surgeries to cease. There simply is no such thing as a perfect surgery and the occurrence of a complication does not mean that that surgery or medical device used in the surgery is defective in design.

The need for repair augmentation in light of the failure of native tissue repairs (NTR) cannot be understated. Surgeons went more than a century performing colporrhaphy procedures with a paucity of scientific literature to inform them of the risks and benefits. In fact, the first randomized control trial involving a colporrhaphy procedure wasn't performed until 2001—more

than 100 years after surgeons began routinely performing this procedure on women. Despite this lack of literature, the surgical community generally understood that the failure rate was high. Weber's 2001 RCT only confirmed this. It found that in the anterior colporrhaphy group, only 30% of patients had satisfactory outcomes. While Weber and colleagues reassessed their anatomic success criteria in this study roughly ten years later, the fact remains that prolapse is exceedingly difficult to successfully treat in the long term without a graft material to augment the already weakened native tissue-based repairs.

Multiple Studies have demonstrated that the rate of prolapse recurrence is extremely high: approximately 40% regardless of approach, as demonstrated in the OPTIMAL (Operations and Pelvic Muscle Training in the Management of Apical Support Loss) trial by Barber and colleagues.[41] Also of note is that the authors of that clinical trial shared data from the 5-year follow-up at the Society of Gynecologic Surgeons Annual Scientific Meeting 2018, Orlando, Florida)., showing failure rates progressing to 70% for sacrospinous ligament fixation and 61% for uterosacral ligament suspension. Such data highlights the fact that NTR is not durable enough to meet the needs of patients, and that graft augmentation must be considered. For patients at increased risk of prolapse recurrence, using transvaginal mesh ("TVM") is a minimally invasive approach and is an excellent option for mesh augmentation. The importance of meticulous surgical technique cannot be emphasized enough as avoiding adverse events during placement of TVM depends largely on optimal surgical technique.[42]

Many studies have looked to see if there truly is a measurable advantage of TVM over NTR. A 2016 Cochrane review by Maher and colleagues included 37 randomized trials (4,023 women) that compared TVM and biologic grafts with NTR.[43] Three primary outcomes were defined: awareness of prolapse, recurrence, and repeat surgery. Compared with women treated with NTR, those treated with synthetic nonabsorbable TVM exhibited a greater reduction in awareness of prolapse (risk ratio [RR], 0.66; 95% confidence interval [CI], 0.54-0.81), decreased recurrence in the anterior compartment (RR, 0.33; 95% CI, 0.26-0.40), and decreased reoperation for prolapse (RR, 0.53; 95% CI, 0.31-0.88). The overall calculated exposure rate was 12%, with a range of 3.2% to 20.8%.[44] Such a wide range is most likely due to a suboptimal, split-thickness dissection. There were no differences in other key secondary outcomes, including dyspareunia, operating time, and estimated blood loss.[45]

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[41] Barber MD, Brubaker L, Burgio KL, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Pelvic Floor Disorders Network. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. JAMA. 2014;311(10):1023-1034

[42] Jambusaria LH, Murphy M, Lucente VR. One-year functional and anatomic outcomes of robotic sacrocolpopexy versus vaginal extraperitoneal colpopexy with mesh. Female Pelvic Med Reconstr Surg. 2015;21(2):87-92

[43] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database System Rev. 2016:CD012079

[44] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database System Rev. 2016:CD012079

[45] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Marjoribanks J. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database System Rev. 2016:CD012079

Further support for TVM can be seen in several longitudinal studies. Meyer and colleagues reported that patients had continued significant improvements in both subjective and objective outcomes.[46] in a study of 5-year follow-up after TVM placement, with a mesh exposure rate of 6%, ,which was attributed to severe vaginal atrophy.[47] A 10-year observational study by Weintraub and colleagues demonstrated a recurrence rate of only 2.6% in the anterior compartment, 7.6% in the posterior (nonaugmented) compartment, and no exposures or extrusions after anterior TVM placement.[48]

Not all data supports a quantifiable benefit of TVM over NTR. The In the 2017 PROSPECT (Prolapse surgery: Pragmatic evaluation and randomized controlled trials) trial, Glazener and colleagues found no difference in desired outcomes with TVM compared with NTR.[49] with an overall 6% to 7% exposure rate over 2 years.[50] This study did not study a formalized standardized technique. The described procedure involved a nonabsorbable mesh inlay to support stitches without mention of any type of level 1 support. (APICAL) . Nor did the break down surgeon experience with 20% of the cases carried out by "registrars," which are the equivalent of U.S. residents or fellows.[51] Such ill defined graft utilization with no apical attachment of the mesh to the sacrospinous ligament.[52] sets the stage for surgical failure as apical involvement must be incorporated if indicated. Such data from The PROSPECT study reinforces the need for the standardization of the TVM procedure.[53] It should be noted The PROSPECT investigators readily admitted what the study was not: a trial conducted "exclusively by the most experienced surgeons in the highest volume centres with a highly protocolised technique."

TVM VS. Sacrocolpopexy

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[46] Meyer I, McGwin G, Swain T, Alvarez MD, Ellington DR, Richter HE. Synthetic graft augmentation in vaginal prolapse surgery: long-term objective and subjective outcomes. J Minim Invasive Gynecol. 2016;23(4):614-621

[47] Meyer I, McGwin G, Swain T, Alvarez MD, Ellington DR, Richter HE. Synthetic graft augmentation in vaginal prolapse surgery: long-term objective and subjective outcomes. J Minim Invasive Gynecol. 2016;23(4):614-621

[48] Weintraub AY, Friedman T, Baumfeld Y, Neymeyer J, Neuman M, Krissi H. Long‐term functional outcomes following mesh‐augmented posterior vaginal prolapse repair. Int J Gynecol Obstet. 2016;135(1):107-111

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[50] Glazener CM, Breeman S, Elders A, et al; PROSPECT Study Group. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). Lancet. 2017;389(10067):381-392

[51] Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomized controlled trials within Comprehensive Cohort Study. PROSPECT study protocol. The National Institute for Health Research. Accessed January 17, 2018 at https:// www.journalslibrary.nihr.ac.uk/programmes/hta/076018.

[52] Clinical and cost-effectiveness of surgical options for the management of anterior and/or posterior vaginal wall prolapse: two randomized controlled trials within Comprehensive Cohort Study. PROSPECT study protocol. The National Institute for Health Research. Accessed January 17, 2018 at https:// www.journalslibrary.nihr.ac.uk/programmes/hta/076018.

[53] Glazener CM, Breeman S, Elders A, et al; PROSPECT Study Group. Mesh, graft, or standard repair for women having primary transvaginal anterior or posterior compartment prolapse surgery: two parallel-group, multicentre, randomised, controlled trials (PROSPECT). Lancet. 2017;389(10067):381-392

This comparative question was answered well by a study by Lucente where they completed a 1-year retrospective cohort study comparing robot-assisted laparoscopic sacrocolpopexy ("RALS") with TVM in a total of 86 patients, with both approaches performed by the same surgeon. Having the same experienced surgeon perform two separate techniques in a statistically similar population with the ability to study the outcomes is a powerful tool. In this study both treatment groups showed statistically significant improvements in nearly all functional and quality-of-life measures, including urinary symptoms, sexual function, and POP-Q scores.[54] Additionally, points Aa and Ba on the POP-Q score were significantly improved with TVM as compared to RALS. Such data reaffirms the belief that both later and apical support can be obtained through TVM utilization as opposed to sacrocolpopexy,which only addresses the apex.[55] Such a finding is truly relevant given DeLancey and colleagues' dynamic magnetic resonance imaging study, which demonstrated advanced prolapse results from both lateral and apical detachment.[56] Additional support for TVM over RALS can be seen in surgical time where TVM placement also was faster than RALS by approximately 96 minutes and could be performed using regional anesthesia. It should be noted that both arms in this study featured a single mesh exposure[57]

Further support for TVM in comparison to abdominal graft augmented procedures can be seen in the work of Gutman and colleagues where they compared laparoscopic mesh hysteropexy with TVM. They were able to show cure rates that were comparable and significantly longer operative times in the laparoscopic approach (174 vs 64 minutes; $P<.0001$).[58] In terms of graft complications mesh exposure rates of 2.7% for laparoscopy and 6.6% for TVM, were noted. Such a high rate of exposure could be due to improper surgical technique in TVM placement.[59]

TVM outcomes are highly surgeon dependent.

In 2011, the United States Food and Drug Administration ("FDA") issued an update on the safety and efficacy of TVM augmentation and mandated post-market studies.[60] The data contained within that study is not being debated in this statement. Attributing erosions to the molecular make up of mesh is incorrect and not appropriate.

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[54] Jambusaria LH, Murphy M, Lucente VR. One-year functional and anatomic outcomes of robotic sacrocolpopexy versus vaginal extraperitoneal colpopexy with mesh. Female Pelvic Med Reconstr Surg. 2015;21(2):87-92

[55] Jambusaria LH, Murphy M, Lucente VR. One-year functional and anatomic outcomes of robotic sacrocolpopexy versus vaginal extraperitoneal colpopexy with mesh. Female Pelvic Med Reconstr Surg. 2015;21(2):87-92

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[59] Gutman RE, Rardin CR, Sokol ER, et al. Vaginal and laparoscopic mesh hysteropexy for uterovaginal prolapse: a parallel cohort study. Am J Obstet Gynecol. 2017;216(1):38.e1-e11

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Mesh exposure rates reported in the literature vary widely, ranging from 0% to 30%, even when surgeons used identical mesh products.[61] Without any type of doubt such facts support surgical technique as an important contributing variable that must be accounted for along with taking into consideration the "surgeon factor" as a confounder in trials that compare surgical procedures.[62] Studies on TVM have shown that low-volume surgeons had significantly higher reoperation rates, while high-volume surgeons achieved a 41% reduction in reoperations.[63,64] When TVM is performed by expert surgeons, the reported mesh exposure rates for TVM are noticeably lower.[65, 66, 67, 68, 69] Such discrepancy between high and low volume surgeons can be seen in other aspects of gynecology. An essay titled "Doing What is Best for the Patient: When Surgical Volume Matters", by Brown, summarizes many examples of increased complications, morbidity, and resource utilization by low voulume surgeon.[70] Such statements are further supported by other studies.[71]

The most common adverse event of TVM is mesh exposure thus decreasing its frequency woud improve the safety profile of graft augmented prolapse surgery. The most important step to successful TVM placement is the initial dissection. Gynecologists traditionally have performed a split-thickness, colporrhaphy-style dissection to place the mesh within the layers of the vaginal wall.[72] Placement within these planes, however, is too superficial and increases the risk of exposure. By contrast, consistent performance of a full-thickness vaginal wall dissection

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[66] Meyer I, McGwin G, Swain T, Alvarez MD, Ellington DR, Richter HE. Synthetic graft augmentation in vaginal prolapse surgery: long-term objective and subjective outcomes. J Minim Invasive Gynecol. 2016;23(4):614-621

[67] Weintraub AY, Friedman T, Baumfeld Y, Neymeyer J, Neuman M, Krissi H. Long term functional outcomes following mesh‐augmented posterior vaginal prolapse repair. Int J Gynecol Obstet. 2016;135(1):107-111

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and placing the mesh in the true vesicovaginal space[73], allows surgeons to achieve a TVM exposure rate as low as 0% to 3%.[74,75]

Development of Prosima

Polypropylene sutures have been used in surgery since the 1950s. In 1969 the FDA approved Prolene sutures as safe and effective. Prolene is a polypropylene based monofilament infused with proprietary additives that effectively counteract any oxidative degradation. Half a century of clinical use in nearly every surgical application worldwide has demonstrated the superb biocompatibility of Prolene for implantation in the human body. Prolene has been used as a hernia mesh since the 1970s and has been used utilized for two decades as the sling material for the TVT line of mid-urethral slings. In 2018 AUGS, SUFU, ACOG and IUGA along with multiple other professional societies endorsed the safety, efficacy and biocompatibility of polypropylene based mesh:

> Polypropylene material is safe and effective as a surgical implant. Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years.[76]

I agree with this statement, while acknowledging that the mesh utilized in Prosima is constructed differently than the Prolene mesh used in the TVT products. In 2002, the FDA cleared Gynemesh PS, which was a sheet of monofilament, macroporous, Prolene Soft mesh, which was constructed with a larger pore and lighter weight than the mesh used in the sling products. This mesh was intended to be used to augment prolapse repairs, to include vaginal

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[75] van Raalte HM, Lucente VR, Molden SM, Haff R, Murphy M. One-year anatomic and quality-of-life outcomes after the Prolift procedure for treatment of posthysterectomy prolapse. Am J Obstet Gynecol. 2008:199(6):694.e1-e6

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approaches. Prolene Soft mesh was knitted to allow for elasticity in both directions in order to accommodate the varying stress loads encountered in the body. As classified by Amid, it is a Type I mesh with pores around 2500 microns, which allows for superb tissue in-growth and the pass-through of leukocytes and macrophages.[77] It is important to note that long before Prolene Soft or Prolene mesh were used, surgeons had been using mesh materials for decades. In 1955, Moore and colleagues noted the use of tantalum mesh to repair cystoceles.[78] See also Lane 1962[79], Baker KR, et al. 1990[80]; Benson 1996[81]; Julian 1996[82]; Migliari 2000[83] and Berrocal 2004[84].

In light of the high failure rates of native tissue repairs I have discussed above, surgeons were looking for a more durable and standardized method to treat POP. While surgeons increasingly adopted the use of mesh to treat POP in the 1990s and early 2000s, a group of surgeons in France (the "TVM" group) sought to develop a standardized transvaginal approach to repair prolapse using a polypropylene mesh. This effort led to the development of Prolift, which used the mesh in Gynemesh PS. Prolene Soft mesh was a "carefully selected and tested synthetic material."[85]

The efforts of the TVM group ultimately led to Prolift, which was first marketed by Ethicon in March 2005. This product came either as a 4 armed anterior pre-cut mesh implanted via the obturator approach, a 2 armed posterior pre-cut mesh secured in the sacrospinous ligament through a trans-gluteal approach, or Prolift Total, which included both the anterior and posterior meshes. In addition to having the mesh pre-cut, Prolift introduced standardized tools (a Guide, Cannula, and retrieval device) and an IFU (instructions for use) that provided detailed directions to implant the product. Importantly, the implantation of Prolift required full-thickness vaginal incisions for proper placement.

Following the launch of Prolift, Ethicon sought to develop a similar kit-based product to treat prolapse but one that was technically less demanding. In conjunction with Dr. Marcus Carey, an Australian surgeon, Ethicon developed Prosima. Prosima lacked the long anchoring

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[85] Berrocal J, Clave H, Cosson M, Debodinance P, Garbin O, Jacquetin B, Rosenthal C, Salet-Lizee D, Villet R. Conceptual Advances in the Surgical Management of Genital Prolapse. The TVM Technique Emergence. J Gynecol Obstet Biol Reprod 2004;33:577-587

arms of Prolift and instead deployed a vaginal support device to ensure proper mesh fixture and tissue integration. It was intended for use in stage II and III prolapse and utilized Gynemesh PS mesh, just as Prolift did. Also like Prolift, it came with an anterior mesh, a posterior mesh, or both. However, unlike Prolift, Prosima, as noted above, lacked arms and was not placed with trocars. No exit points were required, Prosima required fewer surgical steps than Prolift, and was a less invasive procedure. Operation and recovery times were relatively low with Prosima. All of these were the intended (and actual) benefits of the product.

Importantly, Ethicon did not rush Prosima to market. It was cleared by the FDA in February 2007 but wasn't widely launched until 2010. During the interim, Ethicon conducted a one year clinical study led by Dr. Zyczynski to ensure its safety and efficacy.[86]

Gynemesh PS / Prolift studies

In a 2004 study, Lucente concluded that Gynemesh PS "is safe, with a low rate of significant mesh-related complications."[87] In this 160 patient study, Lucente went on to find a 10% erosion rate and a success rate of 76%. Ali et al. noted even better results in a 2006 anterior study in which they found a recurrence rate of 6.6% and an exposure rate of 6.5%.[88] In 2006, Sola conducted a study involving 42 Gynemesh PS procedures in both the anterior and posterior compartments.[89] He reported no post-operative complications and a success rate of 95% in the anterior compartment and 100% in the posterior compartment. Al-Nazer et al. found in a 2007 study that evaluated 40 patients undergoing either an anterior colporraphy or prolapse repair involving Prolene Soft, that while improvement was noted in both groups, the Prolene Soft arm proved superior with 95% improvement compared to 70% for the anterior arm.[90] Gynemesh PS has also been studied in the context of laparoscopic sacral colpopexy. Agarwala found in 2007 a subjective and objective cure rate of 97% and 100% with no reports of mesh exposure.[91]

Natale et al. performed an RCT in 2009 between Gynemesh PS and Pelvicol with a two year follow up.[92] The Gynemesh PS arm showed that the number of patients experiencing pre-operative dyspareunia dropped from 20 to 10 patients. Moreover, the exposure rate in the Gynemesh PS arm was 6.3% while the cure rate was 71.9%. In 2011 Miller et al. performed a

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five year follow up study on Gynemesh PS patients.[93] They found that only one patient reported pain at five years and only one patient who was sexually active before her surgery reported de novo dyspareunia.

Dr. Carey conducted an RCT of Gynemesh PS in 2009 comparing anterior and posterior repair using mesh versus a corporrhaphy repair.[94] Both groups showed patient satisfaction, but the mesh group yielded a higher success rate at one year: 81% compared to 65%.

Prolift, which utilizes the same mesh as Prosima, was the most studied device to treat prolapse. Numerous RCTs evaluated its safety and efficacy. Withagen et al. conducted an RCT in 2011 between a conventional repair and Prolift.[95] At one year follow-up, the study found that 45.2% of patients who underwent a conventional repair experienced failure while only 9.6% of Prolift patients experienced failure. 16.9% of the Prolift patients experienced a mesh erosion, but nine out of the fourteen patients with an erosion were asymptomatic and only required local estrogen treatment. In both arms of the study, dyspareunia improved and there was no meaningful difference between the two groups in terms of de novo dyspareunia.

Other RCTs have also confirmed the superiority of Prolift compared to native tissue repair: Halaska 2012[96]; Svabik 2014[97]; Sokol 2012[98]; and da Silveira 2015.[99] Longer term studies also demonstrate the superior durability of Prolift. In 2012, Benbouzid conducted a 4.5 year follow-up study that found a 85.3% cure rate with a mesh exposure rate of 5.3%.[100] De

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[97] Svabik K, Martan A, Masata J, El-Haddad R, Hubka P. Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014; Apr;43(4):365-71

[98] Sokol AI, Iglesia CB, Kudish BI, Gutman RE, Shveiky D, Bercik R, Sokol ER. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Amer J Obstet Gynecol 2012;206:86.e1-9

[99] da Silveira SDRB, Haddad JM, de Jarmy-Di Bella ZIK, Nastri F, Kawabata MGM, da Silva Carramao S, Rodrigues CA, Baracat EC, Auge APF. Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int UrogynecoI J 2015;26:335-342

[100] Benbouzid S, Cornu JN, Benchikh A, Chanu T, Haab F, Delmas V. Pelvic organ prolapse transvaginal repair by the Prolift system. Evaluation of efficacy and complications after a 4.5 years follow up. Int J Urol 2012;19:1010-1016

Landsheere conducted a three year study in 2012 as well and found low complication rates with a 11.6% re-operation rate.[101]

Prosima Studies

The clinical studies conducted on the Prosima device also support its safety and efficacy. Dr. Marcus Carey conducted a Gynemesh PS study in the shape similar to Prosima that utilized the VSD.[102] At one year follow-up, only four mesh erosions were observed and objective and subjective success rates were 85% and 87%, respectively. And while 58% of patients claimed sexual dysfunction before their surgery, only 23% of patients reported the same at one year follow-up. In terms of the VSD, the authors noted that it supported "not only the vaginal tissues after surgery but also the positioning of the mesh until incorporation into the body tissues occurs, it is possible to avoid placing sutures into the sacrospinous ligaments or paravaginal spaces."

Prior to the launch of Prosima, Reisenauer et al. conducted a cadaver study in 2009 using Prosima which confirmed the safe anatomical passage and placement of the device.[103]

As mentioned above, Zyczynski et al. conducted a 12 month study on Prosima that was sponsored by Ethicon and published in the American Journal of Obstetrics and Gynecology.[104] The study involved 130 women and found a success rate of 76.9% when anatomic success was measured as POP-Q stage 0/I. When success was defined as above the level of the hymen, the rate was 86.9%. The study emphasized the importance of not removing the VSD too early and found that pain associated with the VSD during the 3-4 weeks it was in the body to be extremely minimal. Significantly, out of the 11 women who reported dyspareunia before their Prosima surgery, 9 had resolution of that problem at one year. Only three patients reported de novo dyspareunia. Also of significance was the fact that complications following Prosima were relatively low. Only 8% of patients experienced a mesh exposure, 1.3% experienced UTIs, 4.1% experienced SUI and only 2.2% required surgical re-intervention for prolapse. Patients in this study also reported significant improvements in their quality of life.

This same cohort of patients was followed up at 2+ years by Sayer et al.[105] Complications still remained low with only one additional erosion, one additional patient experiencing SUI and only two new surgical interventions. When anatomic success was defined

[101] De Landsheere L, Ismail S, Lucot JP, Deken V, Foidart JM, Cosson M. Surgical intervention after transvaginal Prolift mesh repair Retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012;206:83.e1-7

[102] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391–397

[103] Reisenauer C, Shiozawa T, Huebner M, Carey M. Anatomical cadaver study of pelvic floor reconstruction using a new polypropylene implant vaginal repair system and a vaginal support device. Int Urogynecol J 2009;20(suppl 2):S200

[104] Zyczynski HM, Carey MP, Smith ARB, Gauld JM, Robinson D, Sikirica V, Reisenauer C, Slack M. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Amer J Obstet Gynecol 2010;203:587.e1-8

[105] Sayer T, Lim J, Hinoul P, Gauld J, Van Drie D, Slack M. Medium-term clinical outcomes following surgical repair for vaginal prolapse with a tension-free mesh and vaginal support device. Int Urogynecol J 2011;22(suppl 1):S89

as POP-Q stage 0/I, 69.1% of patients met criteria; however, when success was defined as above the level of the hymen, 84.5% met criteria. This study also demonstrated the importance of leaving the VSD in place at least 21 days. Patients who had it removed earlier had drastically lower success rates. Sexual function was also shown 2+ years out to improve from baseline and statistically significant improvements in quality of life were also observed. Mesh exposure was noted to be at 9.1% with most exposures occurring in the first six months.

Khandwala et al. performed a Prosima study involving 94 women in 2011.[106] They found a 82.7% success rate with a 5.3% erosion rate and only 2 reports of de nova dyspareunia. Sing et al. found results in their study supporting the safety and efficacy of Prosima. At one year follow-up, 116 were assessed. 92.2% were cured with success being defined at the level of the hymen and no need for surgical re-intervention. Mesh exposure was only 2.6% and patients experienced statistically meaningful improvements in both quality of life and sexual function.

Complications

Prolene meshes, including Gynemesh PS are safe, effective and highly biocompatible and have demonstrated long term durability with relatively low complication rates. This is especially true when used in the hands of an experienced, skilled surgeon. In my practice I have implanted thousands of patients with either Prolene mesh or Gynemesh PS and have seen great success with few patients presenting with short- or long-term mesh-related complications. More importantly, as reflected in the medical literature I've described above, my experience is supported by what has been reported in peer reviewed publications. Complications that patients experienced following implantation of Prosima are usually functions of how that implant surgery was performed and not related to the device itself.

All surgeries carry with them inherent potential for complications—some severe and some long-term. Basic, elemental risks of any pelvic surgery include but are not limited to the following: pain, dyspareunia, infections and/or abscesses, urinary problems, fistulae, scarring, inflammation, injury to organs, vessels or nerves, groin pain, herniation, hematoma formation, recurrence (failure of the operation), bleeding, and even death.

Pelvic pain and dyspareunia specifically are extremely common events in post-menopausal patients. As far back as 1996, Jamieson and Steege found a 46% dyspareunia rate in the sample group, with 45% of the patients experiencing pain for more than one year.[107] 39% of patients in the same study reported pelvic pain. Ellerkmann in 2001 found similar results.[108] In short, these problems frequently happen regardless of whether the patient has had mesh surgery and are often caused by an array of problems ranging from atrophy, prior surgeries, and pelvic floor dysfunction as evidenced by chronic pelvic muscle spasms.

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[106] Khandwala S, Slack M, Hinoul P, Urquhart C, Al-Salihi S. A trocar-free procedure for vaginal Prolapse repair using mesh and a vaginal support device - an observational registry. Fem Pelv Med Reconstr Surg 2011 Oct;17(5):S164

[107] Jamieson DJ1, Steege JF. The Prevalence of Dysmenorrhea, Dyspareunia, Pelvic Pain and Irritable Bowel Syndrome in Primary Care Practices. Obstet Gynecol. 1996 Jan;87(1):55-8

[108] Ellerkmann JM, Cundiff GW, Melick CF, Nihira MA, Leffler K, Bent AE. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol 2001;185:1332-8

Pelvic pain, scarring, and dyspareunia are potential risks of any pelvic surgery and are not unique to mesh surgeries like Prosima. In fact, the potential for pain and dyspareunia has been reported in the medical literature for decades and has been a matter of common knowledge for just as long. (Francis 1961: "Apareunia and dyspareunia are well accepted complications of operations which involve incision and suture of the vagina, and are variously explained;"[109] see also Lane 1962;[110] Haase & Skibsted 1988;[111] Benson 1996;[112] Iglesia's 1997 Review;[113] and Weber 2000).[114] Weber noted in her 2000 study the high dyspareunia rates associated with colporrhaphies. These surgeries are still performed today, despite the high risk of pain or dyspareunia associated with them. The fact that pain or dyspareunia may follow a surgery, to include mesh-based repair like Prosima, does not mean that either the surgery or the device being used in that surgery is defective in design.

The RCTs I noted above that evaluated Gynemesh PS to native tissue repairs showed no difference in terms de novo pelvic pain, pain, and dyspareunia. Nor did they show differences in change of vaginal length or caliber and sexual function as measured by PISQ scores. In terms of Prosima specifically, the studies cited above demonstrate that Prosima had a net positive effect on sexual function. While it is possible that pain or dyspareunia can follow a Prosima procedure, a patient is actually at a greater risk for these complications if they undergo a traditional native tissue repair.

Plaintiff experts have alleged a number of complications and design defect allegations against Gynemesh PS and Prosima. All of them lack merit. Generally, plaintiff's experts are critical of the vaginal placement of mesh, arguing that the vagina is a "clean contaminated field" and that the placement of a mesh vaginally increases the likelihood of infections and heightens the foreign body response and inflammation that follow mesh placement. This is not supported by clinical experience or the weight of the medical literature. Were this argument true, the vast majority of patients who had a transvaginal mesh would experience infections and other mesh related complications. This simply is not the case. Infections following mesh placement are actually quite rare and usually associated with mesh exposure—a complication that can follow any mesh procedure to include the current 'gold standard' abdominal sacrocolpopexy.

Plaintiff experts have also alleged that the Prolene material itself degrades. This also lacks merit and is not true. Prolene polypropylene is highly stable and does not degrade within the body. Claims that mesh fibers show "cracking" at high magnifications reflect a failure to

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[109] Francis WJA, Jeffcoate TNA. Dyspareunia following vaginal operations. J Obstet Gynaecol Br Commonw 1961 Feb;68:1-10

[110] Lane FE. Repair of posthysterectomy vaginal-vault prolapse. Obstet Gynecol. 1962 Jul;20:72-7

[111] Haase P, Skibsted L Influence of operations for stress incontinence and/or genital descensus on sexual life. Acta Obstet Gynecol Scand. 1988;67(7):659-61

[112] Benson JT, Lucente V, McClellan E. Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with longterm outcome. Amer J Obstet Gynecol 1996;175:1418-2

[113] Iglesia C. The Use of Mesh in Gynecologic Surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8(2):105-15

[114] Weber AM, Walters MD, Piedmonte M R. Sexual function and vaginal anatomy in women before and after surgery for pelvic organ prolapse and urinary incontinence. Am J Obstet Gynecol 2000; 182:1610-5

properly clean explanted mesh specimens (Thames 2017).[115] Moreover, I agree with AUGS / SUFU 2014 FAQ that address this issue:

> Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with "cracked" surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure.

There is no medical literature in existence that supports the claim that there is any Prolene degradation of any clinical significance. Based on my extensive experience, which includes explanting mesh materials and my review of the medical literature and professional society position statements, I believe that the mesh used in Prosima does not degrade or otherwise cause any degradation-related complications.

Plaintiff experts also contend that meshes like Gynemesh PS are cytotoxic and elicit an excessive chronic foreign body reaction that causes excessive inflammation, scarring, mesh contracture/shrinkage and therefore pain. This allegation is also without merit and not supported by the weight of medical literature. While all foreign bodies will cause a foreign body reaction and mild inflammation, the high biocompatibility of Prolene mesh has been demonstrated in both clinical experience and the medical literature for decades to produce safe and effective long terms results in patients. Prolene hernia mesh has been safely implanted since the 1970s and mid urethral slings made of Prolene mesh have been implanted now for two decades and are universally recognized as the gold standard treatment. Moreover, Prolene mesh in the form of Gynemesh PS is still being used safely and effectively today in the treatment of apical prolapse through abdominal sacrocolpopexy procedures. To claim that Prolene mesh triggers an excessive foreign body reaction that causes excessive inflammation resulting in contraction and pain ignores all of these realities. Gynemesh PS in Prosima has been shown to be well tolerated as a synthetic implant. While it does induce an acute inflammatory response upon implantation, this is expected and intended to facilitate healthy scar tissue formation essential for healing. Any chronic inflammatory response is mild, natural, and non-symptomatic. Moreover, claims that mesh shrinks or contracts or undergoes pore collapse fails to account for the fact that any mesh shrinkage is an expected and intended function of scar tissue reacting on the mesh. This is something that is specifically warned about in the Prosima IFU.

Plaintiff experts' criticism of the "blind passage" utilized in Prosima is also without merit. Surgeons have always performed surgery based on tactile feedback without direct visualization. This is not a component of surgery introduced by Prosima (or Prolift) and is not

115 Thames SF, White JB, Ong KL. The myth: in vivo degradation of polypropylene-based meshes. Int Urogynecol J 2017; 28:285–297

indicative of a design defect. Many other non-mesh pelvic floor surgeries require the lack of visualization and carry with them the potential risk of organ or nerve damage.

Plaintiff experts have also faulted the pore size and weight of Gynemesh PS. Gynemesh PS is a large pore, lightweight monofilament mesh that, as I have described above, has a long standing history of safety and efficacy as documented by the medical literature. The pores in Prosima are more than sufficient to facilitate healthy tissue integration and the weight of the mesh does not induce an excessive foreign body reaction. In fact, while it was initially hoped that incorporating Ultrapro—a lighterweight mesh than Gynemesh PS—into Prolift +M would reduce complications and increase efficacy, the studies that have looked at this issue have shown no meaningful difference (Quemener 2014).[116]

Any claims by Plaintiff experts that Prolene mesh causes cancer is completely lacking in support from the medical literature. The lack of such reports in the medical literature is striking when one considers that millions of women have been implanted with some form of Prolene mesh.

Plaintiff experts have argued that a number of safer alternative designs to Prosima and Gynemesh PS existed. To the extent they contend that native tissue repairs are safer alternative designs, I disagree. Other surgeries are not alternative designs—they are simply other surgical options for a surgeon. Moreover, I'm aware of no other alternatively designed mesh like Ultrapro or Vypro that would have prevented or significantly reduced the potential complications of mesh erosion, pain, dyspareunia, scarring, contraction, infection and urinary problems during the time that Prosima was on the market. Prosima was safe and effective and was state of the art while it was on the market from 2009 – 2012.

IFU

Prosima's Instructions for Use (IFU) was adequate, helpful, and not misleading in terms of its indications, instructions, and warnings and adverse reactions. It was not intended (nor should it be) to teach surgeons how to perform every surgical technique or inform them of risks or complications that are commonly known throughout the pelvic floor surgical community. Surgeons rely on the education, training, experience and review of the medical literature to understand how to perform good surgical technique and what are the potential risks of performing pelvic floor surgery. Surgeons specifically are also expected to know without reliance on a manufacturer's IFU what are the risks and benefits of performing surgery using mesh. Mesh erosion and exposure is the one truly "unique" risk to performing mesh surgery and Prosima's IFU appropriately warns of this risk. Risk factors that can lead to erosion like atrophic vaginitis, smoking, and too superficial placement of the mesh are all commonly known by surgeons and have been for decades. Moreover, surgeons should not rely on an instructions for use document to inform them about the frequency and severity of particular potential complications. This is information that is integral to a surgeon's education, training, experience, and review of medical literature, and is not something that is expected to be included in an IFU.

[116] Quemener J, Joutel N, Lucot JP, Giraudet G, Collinet P, Rubod C, Cosson M. Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh. 20 months median follow-up outcomes. Eur J Obstet Gynecol Reprod Biol 2014;175:194-198

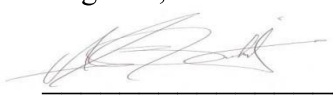
That said, it is noteworthy that Ethicon sponsored Dr. Zyczynski's study in which the risks of mesh exposures, revision procedures, UTIs, cystotomies, de novo urge and SUI, and de novo dyspareunia were all discussed. This study was widely circulated amongst doctors performing Prosima and was an integral part of Ethicon's professional education programs. From my extensive experience proctoring Prosima events on behalf of Ethicon, I can speak to the fact that these events provided great instruction and information about the risks and benefits of Prosima. Complications, including erosion, revision surgery, pelvic pain, dyspareunia, and mesh contracture were discussed at length at these events and Ethicon provided the medical community with information regarding the frequency and severity both.

In 2008[117] and again in 2011,[118] the FDA issued public health notices concerning the use of mesh. These notices discussed various risks associated with the use of transvaginal mesh and serve as yet another source of publically available information that would contribute to a surgeon's understanding of potential complications.

Ethicon also provided patient brochures to doctors to provide to patients regarding Prosima. These brochures provided adequate information to patients about the product and its potential risks (to include pain with intercourse). However, these brochures were never intended to take the place of the risk/benefit informed consent discussion that a doctor should have with his or her patient.

In summary, I believe that Prosima was a safe and effective product to treat pelvic organ prolapse and offered better benefits and outcomes to patients than native tissue repairs. The warnings in the IFU were adequate and appropriately accounted for a surgeon's common knowledge of surgical risks. The design defect allegations of plaintiff experts are without merit as I describe above. The benefits of Prosima outweighed the risks—the success rates were high and the complication rates were low. It was a state of the art product at the time of its launch and I do not know how it could have been made any safer. I hold all of my opinions contained in this report and those found in Exhibit C to this report to a reasonable degree of scientific and medical certainty and base them on my extensive education, training, experience treating thousands of patients, and my review of the medical literature and other materials reflected on my reliance list.

August 6, 2018



Ahmet Bedestani, M.D.

[117] FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence. Issued Oct 20, 2008. http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm

[118] FDA. Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse. Update July 13, 2011. https://www.fda.gov/downloads/medicaldevices/safety/alertsandnotices/ucm262760.pdf